AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 127, No. 3

Printed in U.S.A.

THE RISK FACTORS FOR ARRHYTHMIC DEATH IN A SAMPLE OF MEN FOLLOWED FOR 20 YEARS

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Hinkle, L. E., Jr. (Cornell U. Medical College, New York, NY 10021), H. T. Thaler, D. P. Merke, D. Renier-Berg, and N. E. Morton. The risk factors for arrhythmic death in a sample of men followed for 20 years. *Am J Epidemiol* 1988;127:500–15.

In a sample of 301 men, aged 54–62 years, who were employed in the telephone industry in New Jersey, and who were followed prospectively from 1963/1964 to 1984, 65 of 148 deaths were manifested by the abrupt occurrence of fatal ventricular arrhythmias. On multivariate analysis, the factors present at the initial examination that were significantly related to the subsequent occurrence of arrhythmic deaths were: abnormal patterns of QRS conduction; the level of blood pressure; the number of cigarettes currently being smoked; chronic myocardial ischemia; chronic airway disease; and failure to engage in any exercise or heavy physical activity. Among 28 other potential risk factors representing myocardial disorders, ventricular dysrhythmias, other disorders of cardiac rate, rhythm, conduction, and repolarization, and non-cardiac risk factors (including cholesterol level, serum uric acid level, diabetes mellitus, alcohol intake, general arteriosclerosis, other non-cardiac disease, and social, behavioral, and attitudinal variables), none significantly added to risk for arrhythmic death. The risk factors related to the subsequent occurrence of other deaths, manifested by the gradual development of circulatory failure, were significantly different from the risk factors related to arrhythmic deaths.

arrhythmia; coronary disease; death, sudden; heart block; hypertension; smoking

The problem of sudden deaths among US men is primarily a problem of the abrupt occurrence of fatal ventricular arrhythmias at a time when the integrity of the peripheral circulation has been, up to that moment, adequate to maintain the function of the brain and other organs (1, 2). Because these deaths occur abruptly and often unexpectedly to people who are usually out of reach of immediate resuscitation, the ultimate solution to this problem must lie in the prevention of the arrhythmias.

Although a great deal has been learned about the pathogenesis of sudden cardiac

Received for publication November 18, 1986, and in final form May 13, 1987.

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This work has been supported by funds from the National Heart, Lung and Blood Institute of the US Public Health Service (HL 18776), and by private grants.

The authors acknowledge the assistance of Dr. George Bisgeier and of the staffs of the Medical Department and Benefits Department of the New Jersey Bell Telephone Company for making possible the selection of the sample, the examination of the men, and the follow-up of the participants, and also the assistance of Henrietta Schwartz in the preparation of the manuscript and tables.

deaths, the information available is still not adequate to indicate which combinations of the many factors that have been implicated are most important in causing the ultimate occurrence of the fatal arrhythmia. Most of the studies of the antecedents of sudden death have been based upon autopsies (3–11), upon retrospective information from people who have been resuscitated (10, 12–14), upon samples of patients (5, 8, 15–18), and upon community surveys (4, 6, 7, 11, 13, 19), some of which have been prospective. In these studies, the outcome variable "sudden death" has been defined in various ways, not all of which have been consistent with each other. The investigations that have included data on cardiac arrhythmias, have, in general, been based on samples of survivors of recent acute myocardial infarctions. Some of these have used inadequate samples of electrocardiographic complexes. Most of the investigations have dealt with only a small proportion of the many risk factors that are thought to be important, and few have investigated the interactions between these risk factors.

In an effort to define more precisely the antecedents of sudden fatal arrhythmias, we have carried out a detailed 20-year prospective investigation of the natural history of arrhythmic deaths in 301 men. The important features of this investigation have been its prospective nature; its focus upon a population group at high risk for sudden death (men initially aged 54–62 years); the use of a sample selected in a manner such that the findings can be extrapolated, with some caution, to the general body of US men of the same age; the use of repeated examinations at which information has been obtained relating to each of the major categories of variables that have been thought to contribute to the occurrence of sudden death; the extent of the electrocardiographic data; the use of daily time budgets to quantify the behavior and activity of the participants; the intensive investigation of all of the deaths regardless of their nature or cause; and an attempt to identify which of the large number of variables that are known to be associated with the risk of arrhythmic death do significantly affect this risk, and how these variables interact.

This report describes the relation between the "risk factors" present at the initial examination and the occurrence of arrhythmic deaths among the 301 men during the subsequent 20 years.

Materials and Methods

The sample studied

The sample was selected in a manner such that the findings could be extrapolated to a large segment of the general population of US men. Because the examinations of the men had to be detailed and complex, the sample had to be relatively small in size. In order to have an adequate number of outcome events, the sample was selected from a group in which the incidence of sudden death was high (men aged 54–62 years), with the expectation that the participants would have to be followed for a long time. Because the follow-up period would have to be extended beyond the ordinary time of retirement, the sample was obtained from a population of employed men who would receive a death benefit at the time of their deaths, so that the men and their surviving next-of-kin could be more readily located.

The sample was obtained from an age cohort of men who were born between 1902 and 1908, and who were employed in 1962 in the telephone industry thoughout the state of New Jersey. We determined by survey that the death rate and attack rate for coronary heart disease, and the proportion of sudden deaths attributed to coronary heart disease among the 270,000 men in this industry nationwide, were similar to that among all contemporary US men (20), and we ascertained from records that the age-specific death rate for coronary heart disease among the 1,160 men in the cohort in New Jersey during the years from 1935 to 1962 had been similar to that of all other US men (21). The sample for study was stratified to include equal numbers of work-

men, foremen, supervisors, and managers, and to include men of grammar school, high school, and college education (21). A total of 356 men were designated from the cohort randomly on the basis of the last digit of their social security numbers, invited to meetings in various parts of the state, and asked to volunteer. Of these men, 301 (84.6 per cent) agreed to volunteer and participated fully.

Examinations

Intake examinations were carried out at the New York Hospital/Cornell Medical Center from January 1963 to June 1964. The procedures included a comprehensive, questionnaire-guided, general medical history and physical examination; 6-foot (1.83 m) posteroanterior chest x-ray; 12-lead electrocardiogram; biochemical determinations of serum total cholesterol, serum uric acid, glucose tolerance, and serum triglycerides; hemogram and urinalysis; detailed assessment of smoking experience, alcohol intake, and daily time budgets; a battery of psychological tests designed to explore relevant indicators of the activity, behavior, and "hostility" components of Type A and Type B behavior patterns; and an eight-hour tape recording of the electrocardiogram, made under standard conditions of activity and food intake (22–25).

The data collected

An attempt was made to obtain data on all of the major factors thought to be associated with the risk of sudden death in US men between the ages of 50 and 80 years. Potential risk factors for this analysis were identified from the medical literature and from the experience of this study during the first 10 years. The information that could be obtained was constrained by the technologic limitations of non-invasive cardiovascular diagnostic procedures in the 1960s when the studies began; by the cost of carrying out repeated comprehensive examinations; and by the fact that some meaningful indicators of risk (e.g., high density lipoprotein-low density lipoprotein ratios) had not been recognized at that time.

Three categories of cardiac risk factors were originally selected as potentially relevant to determining that a cardiac death would be "sudden": myocardial risk factors, ventricular dysrhythmias, and other disorders of heart rate, rhythm, conduction, and repolarization.

Eight categories of non-cardiac risk factors were selected also, as potentially relevant to the occurrence of heart disease or other conditions that might lead to "sudden cardiac death": metabolic; vascular; intake; pulmonary; other diseases; social and demographic; behavioral; and indications of "impatience," "pressure of time," and "emotional tension." The risk factors are listed in tables 1 and 2.

Other variables that were studied were episodes of syncope, medications taken, and features of events that precipitated death. These variables are not included in this report.

The methods by which the observational data pertaining to the risk factors were collected, the laboratory analyses, and the definitions and criteria used for their identification and classification have been described in detail in other publications (22, 27).

Follow-up of the participants

The men were followed for 20 years. At intervals throughout the observation period, participants were re-examined by us, and were followed with questionnaires and interviews and reports of examinations by private physicians and employers, and copies of electrocardiographic tracings and reports of diagnostic procedures were obtained. All deaths and major illnesses were investigated in detail, and a comprehensive follow-up of all of the survivors was carried out at the end of the observation period.

The methods by which the deaths were investigated have been described in detail (27). The data obtained included copies of death certificates; interviews with next-of-kin, other witnesses, and attending physi-

TABLE 1

Prevalence of cardiac risk factors as graded and categorized at initial examination of 301 randomly selected men, aged 54–62 years, in New Jersey, 1963–1964

Risk factors*	No. of men by category no.			
	3	2	1	0
Myocardial				
MI in past (clinical and/or ECG evidence)†	11	24	37	227
Chronic ischemia (angina pectoris and/or ECG evidence)†	13	45	85	158
LVH pattern on ECG†	0	4	45	245
Cardiac dilatation (x-ray evidence)†	1	5	10	283
Myocardial failure (clinical evidence)‡	4			297
Ventricular dysrhythmias				
VPCs/1,000 complexes§	26	56	95	111
Early cycle R-on-T VPCs‖			16	274
VPC pairs‖			35	254
VPC "runs" (3 or more complexes) ("PVR")‖			11	278
"Q form" VPCs‖			56	233
Other disorders of rate, rhythm, conduction, or repolarization				
Heart rate during six hours of standard activity, mean ± SD		84.46 ± 12.48		
SPCs/1,000 complexes§	18	20	178	70
Disorders of supraventricular pacemaker‖			24	264
PR conduction¶	2	14	11	274
Duration of QRS complex**	7	10	77	207
Abnormal patterns of QRS conduction††	7	9	31	254
QRS axis, frontal plane‡‡	17	14	22	243
QT corrected (Bazett)§§ (26)		2	9	290

* Abbreviations: AVB, atrioventricular block; ECG, electrocardiogram; LVH, left ventricular hypertrophy; MI, myocardial infarction; PVR, paroxysmal ventricular rhythm; SD, standard deviation; SPC, supraventricular premature complex; VPC, ventricular premature complex.

Grading of variables: † Graded: "Definite," 3; "probable," 2; "possible," 1; "none," 0. ‡ Only "definite" evidence considered as positive. § Graded: ≥10/1,000, 3; 1–9.99/1,000, 2; <1/1,000, 1; none, 0. ‖ Graded: "present," 1; "not present," 0. ¶ Graded: 2:1 AVB or higher grades, 3; 1° AVB, constant, 2; 1° AVB, transient, 1; no abnormality, 0. ** Graded: ≥0.12 second, constant, 3; 0.10–0.11 second, constant, 2; ≥0.10 second, transient (on tape recording), 1; none, 0. †† Graded: left bundle branch block, peri-infarction block, or intraventricular block, 3; right bundle branch block, 2; S1S2S3 or RSR′ in V1, 1; none, 0. ‡‡ Graded: 120°–315°, 3; 105° or 330°, 2; 345° or 90°, 1; 0°–75°, 0. §§ Graded: ≥465 msec, 2; 440–464 msec, 1; ≤439 msec, 0.

cians; records of hospitals and physicians; medical examiners' reports, reports of autopsies, and reports of rescue squads.

The outcome variables

The fatal outcome variables were defined in terms that made it possible to determine whether or not they were probably initiated by acute ventricular arrhythmias (28).

"Cardiac death" was considered to have occurred when the rhythmic contractions of the ventricles ceased and did not resume spontaneously.

"Cardiac deaths" were considered to be of two kinds, "arrhythmic deaths" and "deaths in circulatory failure."

An "arrhythmic death" was considered to have occurred when the rhythmic contractions of the ventricles ceased abruptly at a time when the pumping action of the heart was adequate to maintain the peripheral circulation.

A "death in circulatory failure" was considered to have occurred when the rhythmic contractions of the ventricles did not cease until after the peripheral circulation had collapsed.

The criteria that were utilized for determining whether a death was an arrhythmic death or a circulatory failure death have been described in detail elsewhere (27, 28).

An "arrhythmic death" was considered to have occurred when a conscious person or a person who was sleeping and readily arousable was directly observed to lose consciousness suddenly and to collapse abruptly and no evidence of a pulse or heart beat could be detected thereafter.

When a death was not witnessed directly, but the circumstances of the death and the position, condition, and evident activities

TABLE 2

Prevalence of non-cardiac risk factors as graded and categorized at the initial examination of 301 randomly selected men, aged 54–62 years, New Jersey, 1963–1964

Risk factors	No. of men by category no. 4	3	2	1	0
Metabolic					
Body build (ponderal index)*			61	209	30
Glucose tolerance†			11	14	276
Clinical gout‡				11	290
Serum uric acid (mg/dl) (mean ± SD)			5.69 ± 1.74		
Serum cholesterol (mg/dl) (mean ± SD)			243.4 ± 38.1		
Vascular					
Arteriosclerosis other than coronary arteriosclerosis§			10	25	266
Blood pressure					
Systolic (mmHg) (mean ± SD)			145.0 ± 20.2		
Diastolic (mmHg) (mean ± SD)			88.0 ± 12.0		
By category‖			102	78	121
Intake					
Cigarettes/day now smoked¶		25	78	20	178
No. of pack-years ever smoked**			171	44	86
No. of alcoholic drinks/day now††		14	43	219	25
Drinking problem now or in past‡‡				12	289
Airway disease§§		2	47	56	196
Other non-cardiac diseases‖‖		15	36	166	84
Social and demographic					
Age (years) at intake (mean ± SD)			57.9 ± 1.9		
Education¶¶		9	81	118	93
Occupational level***		79	46	86	90
Activities and behavior					
Average hours of sleep/day (mean ± SD)			7.77 ± 0.71		
Average hours of exercise/day (mean ± SD)			0.51 ± 0.59		
Men with any exercise†††				162	138
Average work before breakfast/day (minutes) (for men with such work) (mean ± SD)			20.00 ± 14.42		
Men with any such work†††				10	
Travel time to work (minutes) (mean ± SD)			35.8 ± 15.3		
Purposeful activity, not for pleasure ("work")/average working day (hours) (mean ± SD)			9.95 ± 0.85		
Time starting work, working day‡‡‡			88	77	135
Time quitting work§§§			6	84	204
Attitudes and reactions					
Have time to eat breakfast‖‖‖			11	18	263
Feel pressed for time on way to work¶¶¶		11	16	56	217
Annoyed by delays on way to work¶¶¶		14	6	59	220
Feel pressure of time at work****	35	53	159	41	10
Feel pressure of outside activities****	8	4	80	157	23
Feel emotional tension at work††††		25	71	154	49
Feel emotional tension at home††††		6	29	147	115
Feel fatigue at end of day‡‡‡‡	1	10	137	140	8

Grading of variables: * Graded: ≤11.9 (heavy), 2; 12.0–12.9 (medium), 1; ≥13.0 (slim), 0. † Graded: clinical diabetes, 2; impaired glucose tolerance, 1; no impairment, 0. ‡ Graded: present, 1; absent, 0. § Graded: claudication, stroke, aneurysm or arterial occlusion, 2; calcification of aorta on x-ray, 1; no evidence, 0. ‖ Graded: "definite hypertension," blood pressure, systolic ≥160 mmHg, diastolic ≥95 mmHg, either or both, 2; "borderline hypertension," blood pressure, systolic 140–159 mmHg, diastolic 90–94 mmHg, either or both, 1; "normotension," blood pressure ≤139/89 mmHg, 0. ¶ Graded: ≥40/day, 3; 20–39/day, 2; 1–19/day, 1; none, 0. ** Graded: ≥20, 2; 1–19, 1; never smoked cigarettes, 0. †† Graded: ≥5/day, 3; 3–4/day, 2; 1–2/day, 1; none, 0. ‡‡ Graded: yes, 1; no, 0. §§ Graded: severe airway disease, 3; chronic obstructive pulmonary disease, 2; chronic bronchitis, 1; none, 0. ‖‖ Graded by estimated probability of causing death, as ≥10%, 3; 1–9%, 2; <1%, 1; essentially none, 0. ¶¶ Graded: <8th grade, 3; 8th grade, 2; high school graduate, 1; college graduate, 0. *** Graded: workman, 3; first level supervisor (foreman), 2; second level supervisor, 1; manager or executive, 0. ††† Graded: any purposeful physical exercise or heavy activity, 1; none, 0. ‡‡‡ Graded: 0700–0815 AM, 2; 0830–0845 AM, 1; 0900 AM or later, 0. §§§ Graded in relation to regular quitting time as: ≥1 hour later, 2; up to 1 hour, 1; at or before regular time, 0. ‖‖‖ Graded: no time, 2; must eat on the run, 1; adequate time, 0. ¶¶¶ Graded: most of time, 3; more than half of time, 2; less than half of time, 1; almost never, 0. **** Graded: more than I can do, 4; must keep going constantly, 3; must work steadily but can rest, 2; plenty of time, 1; time left over, 0. †††† Graded: "great deal," 3; "usually some," 2; "occasionally some," 1; "rarely any," 0. ‡‡‡‡ Graded: completely fatigued, 4; very tired, 3; tired, 2; slightly tired, 1; no fatigue, 0.

of the decedent indicated strongly that he must have been conscious and have collapsed abruptly, such a death was considered to be a "probable arrhythmic death."

A "death in circulatory failure" was considered to have occurred when a person under observation lost consciousness gradually (although sometimes rapidly) in a setting of increasing circulatory impairment, and when evidence of pulse and heartbeat did not disappear until after the person was unconscious and the blood pressure was not obtainable.

If such a death was not directly observed, but the prior condition of the decedent, the circumstances of the death, and the position and condition of the body strongly indicated that the death had been "in circulatory failure," it was considered to have been a "probable" circulatory failure death.

The moment of death was witnessed directly and witness' descriptions were obtained in 121 cases; in 27 cases, descriptions of the moment of death were not obtained. In 16 of these cases, the condition of the subject within one hour prior to death was ascertained, and in eight cases, the condition within 12 hours prior to death was ascertained; in all of these cases, the circumstances of death and the condition of the body when discovered were also ascertained. These 24 cases were classified on a "probable" basis, 15 as probable arrhythmic deaths and nine as probable deaths in circulatory failure. In three cases, the data obtained were not sufficient for classification.

In cases of abrupt collapse with cessation of the pulse, when resuscitators reported that they found the heart to be in "ventricular fibrillation" or "asystole," and, after electrical defibrillation, succeeded in restoring the cardiac rhythm, the participant was considered, for the purposes of this research, to have experienced a "fatal arrhythmia" at this time. This policy was adopted because this research has been concerned with the conditions and circumstances under which fatal cardiac arrhythmias have occurred, and because the available information indicates that the initial arrhythmia would have been fatal in almost all of the cases had electrical resuscitation not been carried out.

In this report, three outcome variables are considered: arrhythmic deaths, deaths in circulatory failure, and all deaths.

Statistical procedures

Criteria adopted from the medical literature or developed by us were used to grade or rank the data for each risk factor according to the dimension apparently most pertinent to the outcome (22). If evidence of a risk factor was definitely identifiable but was not always present, it was treated as a dichotomous variable, and, for analytic purposes, was coded "present" (code 1) or "not present" (code 0). If a risk factor was present in all cases but variable in some dimension, such as "frequency" or "severity," or if evidence for a risk factor met the established criteria to a variable degree, the observational data were ranked or graded and coded according to the relevant dimension (for example, myocardial infarction, "definite" (code 3), "probable" (code 2), "possible" (code 1), or "no evidence" (code 0)). Continuous data or specific cut-off points were used for measurement data, and were transformed for variables with highly skewed distributions in the study population (e.g., log ventricular premature complex frequency).

When the observational data relating to some of the "risk factors" (such as myocardial infarction or myocardial ischemia) came from more than one source (clinical history, electrocardiogram, electrocardiographic tape recordings), or when data relating to a variable could be considered in two or more formats (e.g., cigarette smoking as number of cigarettes per day now being smoked, or as pack-years ever smoked), each source or format was tested for its relation to survival. The combinations of observational variables that were selected for inclusion in the analyses, and their grading and coding, are indicated in tables 1 and 2.

All of the selected variables in tables 1 and 2 were initially tested against the three outcomes using univariate Cox regression (29) to determine their significance as single predictors of survival time from the initial examination. Arrhythmic death and circulatory failure death were treated as competing risks (30). When estimating the cause-specific hazard function and regression coefficients for arrhythmic death, circulatory failure deaths were treated as censored, along with men alive at the 20-year follow-up, and then vice versa. Men whose deaths were unclassifiable were included in the analyses for all deaths. These results are shown in table 3.

Computations were done using the BMDP program P2L (31). Variables significant at $p < 0.10$ using the score test were submitted to stepwise Cox regression with a $p < 0.05$ inclusion criterion to determine multivariate risk functions for each outcome. This procedure tested the statistical significance of each variable, adjusting for other risk factors with which it might be correlated, in order to produce a more parsimonious model. Final models were calculated using the more accurate maximum partial likelihood ratio method. Multiplicative mean-adjusted second-order interaction terms were tested for all significant main effects.

Some variables originally recorded as continuous or graded were later dichotomized. For example, since approximately half of the men had no exercise at all, and since no gradient of risk was found with the actual average daily number of hours of exercise in the remaining half of the sample, exercise was analyzed as "any" (code 0) versus "none" (code 1). The small number of missing data items among variables included in the final models were approximated from other variables with which they were highly correlated in order to include all 301 men in the analysis. This had a negligible effect on significance levels or regression coefficient estimates.

The predictability of arrhythmic death as a distinct type of death independent of length of survival was investigated by stepwise logistic regression with arrhythmic death (code 1) versus circulatory failure death (code 0) as the dependent variable, using the maximum likelihood ratio method of BMDP program PLR (32). Any variable significant in the arrhythmic death, circulatory failure death, or total death Cox regression models was considered in the logistic model.

Results

Deaths observed

The vital status of all 301 participants and that of 54 of 55 non-participants were determined after 20 years of observation from age 54–62 years to age 74–82 years. The 301 participants experienced 148 deaths; 65 of these deaths were classified as "arrhythmic" and 80 as "in circulatory failure"; three were considered "unclassifiable." The death rate was slightly higher among the 55 non-participants, whose death certificates suggested that they had relatively more circulatory failure deaths than the participants.

Among the 301 participants, 93 per cent of the sudden deaths within one hour and 72 per cent of the out-of-hospital deaths were classed as arrhythmic deaths (27); 56 per cent of the arrhythmic deaths were "sudden deaths" and the remaining 44 per cent terminated acute illnesses that had lasted more than one hour, and therefore were not technically "sudden deaths." Arrhythmic deaths were the terminal event of 64 of 74 cases in which the primary cause of death was considered to be heart disease. The primary cause of death of 70 of 80 circulatory failure deaths was considered to be a condition other than heart disease.

Prevalence of the risk factors

The prevalence of ischemic heart disease in this sample, as manifested by evidence of chronic ischemia or past myocardial infarction, was comparable with the prevalence reported (22) for contemporary men of similar age. However, in this random sample of employed men, most of the car-

diac risk factors that have been found to be significant predictors of sudden death within 1–2 years in samples of persons who have experienced recent myocardial infarctions were represented by relatively few cases. There were only 35 men with definite or probable evidence of previous myocardial infarction. There were 49 men with left ventricular hypertrophy patterns on their electrocardiogram, but only four of these patterns included the ST and T wave abnormalities that have made left ventricular hypertrophy patterns significant indicators of risk of arrhythmic death in other studies (33). There were four men with definite evidence of present or past myocardial failure, 26 with very frequent ventricular premature complexes, 11 with ventricular premature complex "runs" (paroxysmal ventricular rhythm), and 16 with a QRS time ≥0.10 second and abnormal QRS patterns.

Non-cardiac risk factors were relatively more prevalent (table 2). Diabetes mellitus, clinical gout, the mean level of serum cholesterol, the frequency of cigarette smoking, and the intake of alcoholic drinks, all were within the range reported for US men of the age of these men in the early 1960s (22). The prevalences of systolic blood pressure of ≥160 mmHg (25 per cent) and systolic blood pressure 140–159 mmHg (30 per cent) were similar to those reported for contemporary men of similar age (22). Since most of the men in this sample had regarded themselves as healthy prior to their selection for participation in this study, many had not been examined by physicians for a number of years. Of those who were found to have blood pressure ≥140/90 mmHg at the initial examination, 65.5 per cent gave no history of having hypertension; 87.2 per cent of the men who were discovered to have hypertension at the initial examination continued to have elevated blood pressure at subsequent examinations.

Univariate survival analyses

On univariate analysis, the cardiac risk factors significantly associated with subsequent arrhythmic death were among those that have been identified by other studies as being significant: myocardial disorders, ventricular dysrhythmias, and conduction defects (table 3). The most significant myocardial risk factor was chronic ischemia. Early cycle R-on-T ventricular premature complexes were the most significant of the ventricular dysrhythmias, but the frequency of ventricular premature complexes and the presence of pairs and of Q forms (25) were also significant. All of the QRS patterns that were manifested by constantly prolonged QRS conduction (≥0.10 second) were significant; but the patterns of left bundle branch block peri-infarction block, "non-specific intraventricular block," which occurred most frequently in association with events of ischemic or hypertensive heart disease, were more closely associated with subsequent arrhythmic death than was right bundle branch block, which was sometimes not associated with any other evidence of heart disease. The patterns of S1S2S3 and RSR′ in V1, which were usually not accompanied by prolonged QRS conduction, were not significantly associated with arrhythmic death, and were most often associated with evidence suggesting the presence of pulmonary heart disease.

Several of the cardiac risk factors, including past myocardial infarction, runs of ventricular premature complexes, Q-form ventricular premature complexes, abnormal patterns of QRS conduction and left or right deviation of the QRS axis, were significantly associated with the occurrence of death in circulatory failure. This finding can be attributed to the fact that 39 of the 80 men who experienced circulatory failure deaths had definite or probable evidence of heart disease at the first examination, even though heart disease was the primary cause of circulatory failure death in only 10 of the 80 cases. Chronic myocardial ischemia, which was the most significant myocardial risk factor for arrhythmic death, was negatively associated with the subsequent occurrence of death in circulatory failure.

TABLE 3

Risk factors observed at initial examinations of 301 randomly selected men, aged 54–62 years, in New Jersey, and significantly associated with the occurrence of arrhythmic death, circulatory failure death, or any death in 20 years, based on the Score Test in the univariate Cox model

Risk factors*	Variable type†	p value: Arrhythmic death	p value: Circulatory failure death	p value: All deaths
Cardiac				
Myocardial				
MI in past (grade 3)‡	D	0.003	0.039	0.0004
Chronic ischemia	G	0.0002	0.058§	NS‖
Dilatation	G	0.016	NS	0.026
Myocardial failure (grade 3)	D	0.028	NS	0.042
Ventricular dysrhythmias				
Log VPC frequency	C	0.016	NS	0.048
Early-cycle R-on-T VPCs	D	0.0009	NS	0.080
VPC runs (PVR)	D	NS	0.058	0.032
VPC pairs	D	0.067	NS	NS
Q Form VPCs	D	0.034	0.068	0.005
Other disorders of rate, rhythm, conduction, or repolarization				
QRS duration	C	0.0007	NS	0.007
QRS pattern (grade 3)	D	<0.0000	0.005	<0.0001
QRS axis, frontal plane	G	NS	0.011	0.034
Repolarization prolonged	D	0.006	NS	0.044
Non-cardiac				
Metabolic				
Glucose tolerance	G	NS	0.0004	0.002
Serum uric acid	C	0.013	NS	0.072
Vascular				
Arteriosclerosis other than coronary	G	0.004	NS	NS
Systolic blood pressure	C	<0.0001	NS	0.001
Diastolic blood pressure	C	0.0006	NS	0.028
Hypertension by category	G	0.0004	NS	0.010
Intake variables				
Cigarettes/day now smoking	C	<0.0001	0.025	0.0001
Pack-years ever smoked	C	0.0002	0.058	0.0001
Alcoholic drinks ≥5/day	D	0.014	NS	0.007
Airway disease (grade 3 or 2)	D	0.024	NS	0.037
Potentially life-threatening non-cardiac diseases (≥10% risk)	D	0.013	0.005	0.0002
Social and demographic				
Age at intake	C	0.042	NS	NS
Years of education	C	*0.003§*	*0.015§*	*0.0002§*
Occupational level	G	NS	0.007§	0.015§
Activities and behavior: no exercise or heavy physical activity	D	0.0009	NS	0.002
Attitudes and behavior: feel pressure of time at work	G	NS	0.027§	NS

Note: risk factors not listed were not significantly associated with any outcome.
* Abbreviations: MI, myocardial infarction; PVR, paroxysmal ventricular rhythm; VPC, ventricular premature complex.
† D, dichotomous; G, graded; C, continuous.
‡ For grading of variables, see tables 1 and 2.
§ Negative association.
‖ NS, not significant.

The level of systolic blood pressure and the number of cigarettes/day now smoked were the most highly significant non-cardiac risk factors for arrhythmic death on the univariate analyses. Others were no exercise, low level of education, evidence of arteriosclerosis of vessels other than the coronary vessels, the presence of life-

threatening non-cardiac diseases, high levels of serum uric acid, high alcohol intake, airway disease, and age, in that order.

There was a significant negative association between years of education and arrhythmic death.

The non-cardiac risk factors most significantly associated with circulatory failure death were impaired glucose tolerance, cigarette smoking, and life-threatening non-cardiac diseases. Two social variables (years of education and occupational level), and one attitudinal variable (feeling pressure of time at work) were negatively associated with risk of circulatory failure death. No other social, behavioral, or attitudinal variables, except for absence of physical exercise, were significantly associated with either arrhythmic death or circulatory failure death.

All of the risk factors that were significant for total deaths were significant for arrhythmic death, circulatory failure death, or both.

Multivariate survival analyses

The models provided by the Cox regression are shown in table 4. The most significant risk factors for arrhythmic death were the QRS patterns of left bundle branch block, peri-infarction block, and non-specific intraventricular block; the level of systolic blood pressure; and the number of cigarettes now smoked. The absence of any exercise, chronic myocardial ischemia, the severe grades of airway disease, and age at the initial examination also entered the model at less significant levels. Three variables, diabetes mellitus, life-threatening non-cardiac disease, and marked left or right axis deviation on the electrocardiogram were positively associated with the risk of circulatory failure death; and two variables, level of occupation and felt pressure of time at work, were negatively associated with circulatory failure death. The first four variables in the model for all deaths were the same as those in the model for arrhythmic death. Diabetes mellitus and clinical gout also entered this model, as did occupational level, as a negative indicator.

The mean-adjusted cross-product terms in the stepwise Cox regression were used to test for interactions between variables. There were no significant interactions between main effects in either the arrhythmic death or the circulatory failure death model. In the total deaths model, a significant interaction was observed between blood pressure and glucose tolerance and between blood pressure and occupational level, leading to a steeper gradient of risk of total deaths with blood pressure among men with diabetes and a steeper gradient for total deaths with blood pressure among men in the two lowest levels of employment.

Predicting the type of death

When all 14 variables significant for any of the Cox models were entered into a stepwise logistic regression to predict the type of death, as arrhythmic death (coded 1) versus death in circulatory failure (coded 0), ischemia, systolic blood pressure, no exercise, and occupational level were significant (table 5). The model accurately predicted the way that men would die based on the data from the initial examination independently of when during the next 20 years the death occurred. Among the men who died, only one of the 18 whose estimated probability of arrhythmic death was less than 0.20 actually died in that manner, whereas seven of the nine men whose estimated probability of arrhythmic death was greater than 0.80 did experience arrhythmic deaths. The global chi-square of 27.61 with four degrees of freedom was highly significant ($p < 0.0001$).

Discussion

Disorders of intracardiac conduction, which have been recognized for many years as a potential risk factor for sudden death (34) and were found by the present authors (24) and in the Framingham Heart Study (33) to be a risk factor for sudden cardiac death in prospective investigations, ap-

TABLE 4

Cox regression models for arrhythmic death, circulatory failure death, and all deaths, based on data from initial examinations and subsequent 20-year observations of 301 randomly selected men, aged 54–62 years, in New Jersey, at intake in 1963–1964

Variable	Variable type*	Arrhythmic death		Circulatory failure death		Total death	
		Coefficient	*p* value†	Coefficient	*p* value	Coefficient	*p* value
QRS pattern (grade 3)‡	D	3.170	<0.0001			2.853	<0.0001
Systolic blood pressure§	C	0.233	0.0001			0.145	0.0003
No. of cigarettes now smoked‖	C	0.554	0.0003			0.436	<0.0001
No exercise	D	0.726	0.006			0.363	0.038
Chronic ischemia	G	0.312	0.018				
Airway disease (grades 2 and 3)	D	0.715	0.022				
Age at initial examination	C	0.164	0.022				
Diabetes mellitus	G			0.431	0.003	0.308	0.007
Occupational level	G			0.242¶	0.006	0.146¶	0.033
QRS axis, frontal plane (grade 3)	D			0.942	0.005		
Life-threatening non-cardiac disease	D			0.334	0.017		
Felt pressure of time at work	G			0.286¶	0.030		
Clinical gout	D					0.112	0.017
Myocardial infarction (grade 3)	D						(0.079)**
Global chi-square (df)††		152.8 (7 df)		38.4 (5 df)		128.0 (7 df)	

* D, dichotomous; G, graded; C, continuous.

† Based on chi-square test from maximum partial likelihood ratio.

‡ For grading of variables, see tables 1 and 2.

§ Per 10 mmHg change.

‖ Packs/day.

¶ Indicates negative association.

** Only variable with $0.05 < p < 0.10$ in multivariate models.

†† df, degrees of freedom.

TABLE 5

Logistic regression model for arrhythmic death versus circulatory failure death, based on data obtained from the initial examination of 301 randomly selected, employed men from New Jersey, aged 54–62 years, 1963–1964, and subsequent 20-year follow-up

Variable	Coefficient	p value
Systolic blood pressure†	0.260	0.007
No exercise	0.932	0.011
Ischemia, graded	0.557	0.004
Occupation	0.326	0.029
Constant	−5.057	
Global chi-square (4 df)‡	27.6*	

* $p < 0.0001$.
† Per 10 mmHg.
‡ df, degrees of freedom.

peared in this sample as the most significant risk factor for arrhythmic death. In data from the initial examination, they had a higher specificity for arrhythmic death than any other risk factor studied. Six out of seven men who had patterns of left bundle branch block, peri-infarction block, or intraventricular block experienced arrhythmic death within the first six years of observation. The seventh man, who had a peri-infarction block, developed an acute myocardial infarction and survived long enough to be admitted to a coronary care unit, where he received vigorous anti-arrhythmic therapy and died in circulatory failure. In another phase of these investigations, we have found that, among the men who had or developed disorders of intracardiac conduction during the 20-year observation period, 24 of 37 with QRS times ≥0.10 second, seven out of 18 men with patterns showing right bundle branch block, 17 out of 25 men with patterns showing left bundle branch block, peri-infarction block, or intraventricular block patterns, and four out of four men with patterns showing 2:1 atrioventricular block, all died arrhythmic deaths (Hinkle et al., unpublished data).

The special feature of the conduction defects was their high level of specificity for arrhythmic death within six years, despite a low level of sensitivity. By comparison, the ventricular dysrhythmias, as a group, had a lower level of specificity, and an even lower level of sensitivity. Only eight of 16 men with early cycle R-on-T ventricular premature complexes, nine of 26 with ≥10/1,000 complexes, and four of 11 with short runs of three or more ventricular complexes (paroxysmal ventricular rhythms) experienced arrhythmic deaths within 20 years. Ventricular dysrhythmias did not appear in the final models.

The level of systolic blood pressure, the second variable in the arrhythmic death model, was a more sensitive indicator for arrhythmic death than any other variable studied. Seventy-five men with systolic blood pressures ≥160 mmHg at the initial examination accounted for 26 of 65 arrhythmic deaths: and 89 men with systolic blood pressure 140–159 mmHg accounted for 24 such deaths, while 137 men with systolic blood pressures ≤139 mmHg accounted for only 15 arrhythmic deaths. There was no gradient of risk for circulatory failure death in relation to blood pressure.

The number of cigarettes smoked at the time of the initial examination, which was the third variable in the arrhythmic death model, was the second most sensitive indicator of arrhythmic death. A total of 123 men who then smoked cigarettes accounted for 33 arrhythmic deaths, and 25 men who then smoked 40 or more cigarettes per day accounted for 12 arrhythmic deaths.

"Exercise," the fourth variable in the arrhythmic death model, was, for these men aged 54–62 years, usually an activity no more vigorous than walking or playing golf. Rarely, it was tennis or bowling. "Heavy activity" was for them usually an activity such as climbing a utility pole or digging in a garden. The average duration of all of these activities was less than one hour per day per man. Nevertheless, the men who had any such exercise or "heavy activity" had significantly fewer arrhythmic deaths than the men who had none. This remained true even when all men with any clinically evident chronic disease that might prevent them from exercising, including previous

myocardial infarctions, angina pectoris, congestive heart failure, chronic obstructive pulmonary disease, claudication, or any symptomatic life-threatening disease, were removed from the calculations ($p < 0.05$). Whether exercise in this group of men during and after the initial examination did actually have a protective effect against arrhythmic death or whether it simply indicated a greater state of well-being and vigor in those who exercised, is not clear from these data; but exercise as an indicator of lower risk of arrhythmic death was clearly significant. There was, by contrast, no change in risk of circulatory failure death with exercise.

"Definite" or "probable" evidence of chronic myocardial ischemia, which, with previous myocardial infarction, was present at the last examination prior to death in 55 of 65 arrhythmic deaths, and was one of the most characteristic features of arrhythmic deaths at that time, appeared as only the fifth variable in the arrhythmic death model. Fifty-eight men with definite or probable ischemia at the initial examination accounted for only 20 of 65 arrhythmic deaths. This finding is attributable to the fact that most of the cases of acute or chronic ischemia that preceded arrhythmic deaths developed after the initial examination, occurring as "new events" during the 20-year observation period.

The appearance of the higher grades of airway disease in the model for arrhythmic death reflected their high prevalence (49 cases) at the initial examination of these men, many of whom were long-time cigarette smokers, and the propensity of men in this sample with severe airway disease for experiencing sudden arrhythmic deaths.

Even though the age range for the men in the sample (54–62 years) was only eight years at the initial examination, age at the time of this examination appeared as a significant variable in the model for arrhythmic death.

The arrhythmic deaths were a relatively homogeneous group in relation to the conditions that primarily caused their deaths. All but three of them had heart disease prior to death, and 61 of 65 had combinations of ischemic heart disease, hypertensive heart disease, and evidence of pulmonary heart disease. The deaths in circulatory failure, by contrast, were a heterogeneous group. Forty-three died primarily because of neoplasms, 11 because of vascular disease, 16 because of other chronic diseases, and only 10 primarily because of heart disease (27). The risk factors identified by the model for circulatory death reflected the lack of homogeneity in the group. Diabetes mellitus, life-threatening non-cardiac disease, and marked right or left deviation of the QRS axis on the electrocardiogram appeared as positive risk factors for circulatory failure death. The presence of the electrocardiographic variable reflected the fact that, in addition to the 10 men with heart disease who experienced deaths in circulatory failure, there were 38 others in the group who had significant evidence of heart disease, even though some other condition was the primary cause of death. Evidence of ischemic heart disease and of hypertensive heart disease was more prevalent among the men who experienced circulatory failure deaths than among the survivors.

The presence of occupational level as a risk factor negatively associated with circulatory failure death reflects the fact that, in this sample, as in the industrial population from which it was drawn (20), and also in the US population as a whole, death rates decline as the level of income and education rises. In this sample, the men in the higher occupational categories had higher levels of education as well as income, and a significantly lower rate of death, especially for circulatory failure death.

The significant negative association between feelings of pressure of time at work and the occurrence of circulatory failure death appeared to be situational rather than causal. A number of the upper level managers and executives, who stated that they were pressed for time and had more work than they could accomplish, were men

with overall good health and few subsequent circulatory failure deaths, while a number of the men at the lowest levels of employment who were chronically ill and who subsequently experienced a high frequency of circulatory failure deaths, said they felt little pressure on their time.

Other behavioral and attitudinal variables, which had been designed to investigate patterns of excessive and unremitting purposeful activity not for pleasure ("work"), feelings of impatience and pressure of time, and feelings of fatigue, all of which have been related to subsequent myocardial infarction (34), did not reveal any significant or convincing evidence of an association between these and subsequent arrhythmic death or circulatory failure death.

In evaluating the results of these analyses, one must consider that the "risk factors" that were studied were selected initially because of evidence indicating that they were risk factors for sudden cardiac deaths and for the kinds of heart disease—chiefly arteriosclerotic and hypertensive heart disease—that appear to be the underlying antecedents of most of the sudden cardiac deaths that occur among US men. "Death in circulatory failure," as we have defined it, was not a phenomenon that was being investigated specifically from an epidemiologic point of view at the time that these studies began. The risk factors selected for study, therefore, did not include any cardiac risk factors for circulatory failure death that were believed to be specifically related to death in circulatory failure in the same sense that ventricular dysrhythmias or disorders of cardiac conduction were believed to be related to sudden cardiac deaths. The non-cardiac risk factors did, however, include a number that are known to be antecedents of non-cardiac diseases, such as neoplasms, vascular disease, liver disease, and pulmonary disease, which were major causes of circulatory failure deaths. These risk factors included cigarette smoking, arteriosclerosis of vessels other than the coronary arteries, blood pressure, diabetes mellitus, alcohol intake, airway disease, and age. However, smoking, blood pressure, airway disease, and age were more strongly related to arrhythmic death than to circulatory failure death. Only diabetes mellitus was more strongly related to circulatory failure death than to arrhythmic death. The other variables that were related to both kinds of deaths were not discriminating.

The risk factors that were studied have provided an informative and valuable model of the risk of arrhythmic death within 20 years. Since 91 per cent of the sudden cardiac deaths in the sample were arrhythmic deaths, it is reasonable that the analyses should have turned out this way. It is also not unexpected that the model for circulatory failure death, while statistically significant, did not appear to be highly definitive; and it is understandable that the majority of the variables that appear in the model for all deaths are also in the model for arrhythmic deaths, which accounted for a substantial proportion of all deaths. What is probably most important about these models is the extent to which the model for arrhythmic deaths identifies a small number of risk factors that are highly predictive of the outcome arrhythmic death over a period of 20 years and are distinct from the risk factors for circulatory failure death.

This has been an analysis of the factors that were associated with the risk of arrhythmic death over a span of 20 years, based on a single set of observations at one point in time. The cardiac risk factors that ourselves and others have found to be predictive of sudden death over a span of 2–5 years—ischemia, previous myocardial infarction, myocardial failure, left ventricular hypertrophy patterns, ventricular dysrhythmias, and disorders of conduction—were not highly prevalent in this random sample of men at the first examination, because most of the men who would experience arrhythmic death had not yet developed clinical evidence of heart disease at the time of this examination. The cardiac risk factors, though highly specific for ar-

rhythmic death in many cases, were not sensitive indicators of future arrhythmic deaths 10–20 years before the event. The Cox model identified, instead, the highly prevalent non-cardiac risk factors of hypertension and cigarette smoking as the most sensitive indicators of the men who would, in the next 20 years, develop the cardiac conditions that led to arrhythmic death.

It is of interest to consider that the men in this sample were selected from an age cohort of employed men who were in their late fifties in 1962, and that these men shared the "risk factors" of their contemporaries. They had not altered their diet, their smoking, or their daily activities, as later, younger, and better educated Americans appear to have done since that time. Awareness of the importance of the recognition and treatment of hypertension, as well as the availability of efficacious medications, was just beginning to enter into the medical practice of the physicians who then cared for them. The mean serum cholesterol level of the men in the sample, the prevalence of diabetes, gout, and hypertension—including untreated hypertension—and the proportion of the men who still smoked cigarettes were not significantly different from those of contemporary men of similar age, although they were different to some degree. However, there is no important reason to doubt that the significant risk factors for arrhythmic death that were found in this sample are still the significant risk factors in contemporary men. Since elevated blood pressure and cigarette smoking are potentially alterable conditions, and their elimination might reduce the risk of death, even in men of the same age as these men, this observation has some significance.

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